CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-998/S-009 **SUBMISSION DATE:** 6/12/00
PRODUCT: Celecoxib (celebrex) Capsules 100 mg & 200 mg 12/18/00
SPONSOR: Searle
4901 Searle Parkway, Skokie, IL 60077
TYPE OF SUBMISSION: Supplement **REVIEWER:** Sue-Chih Lee, Ph.D.

Synopsis

Two PK studies were included to support safety data submitted in this supplement.

One multiple dose study provided the plasma concentration time profiles of celecoxib given at higher than recommended doses. The results indicate that at high celecoxib doses of 800 mg and 1200 mg BID under fed conditions, mean celecoxib AUC (but not Cmax) was approximately dose proportional to those for the 200 mg dose observed in a previous study.

Another study investigated the bioequivalence of diclofenac sodium 75-mg tablets (manufactured by the sponsor) used in a safety trial (CLASS 2) to the marketed Voltaren 75-mg tablets. In the CLASS 2 trial, a formulation of diclofenac sodium comprised of a 75 mg enteric-coated diclofenac sodium core with placebo outer mantle was used in lieu of the marketed Voltaren tablets to achieve the desired blinding. However, the bioequivalence study shows that diclofenac sodium tablets used in the CLASS 2 trial are not bioequivalent to the Voltaren tablets. According to the sponsor's analysis, mean diclofenace AUC was within the 80-125% range but mean Cmax was lower and mean Tmax was shorter compared to Voltaren tablets. An examination of the data indicated that mean Cmax at the 75-mg dose level for tablets used in the CLASS 2 trial was similar to that for Voltaren tablets at the 50-mg dose level observed in a previous study. The sponsor considers this lack of bioequivalency in diclofenac Cmax not clinically important. We disagree with the sponsor in this regard since there is no scientific evidence to rule out diclofenac Cmax as an important parameter related to safety. Therefore, the safety profile of Voltaren tablets may be worse than what was observed for the diclofenac tablets in the CLASS 2 trial.

Comment

The diclofenac bioequivalence study was conducted using a replicate design. The sponsor was requested to provide the bioequivalence data. Once the data are received, bioequivalence test will be performed by the QMRS of FDA to confirm the sponsor's conclusion that the two diclofenac formulations are bioequivalent in terms of AUC and not Cmax.

Recommendation

From the Office of Clinical Pharmacology and Biopharmaceutics standpoint, the submission is acceptable provided that the sponsor's bioequivalence assessment is in agreement with the Agency's analysis.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. 1/03/01

CC:
NDA 20-998
HFD-550 (Div.File)
HFD-550 (CSO/Kong)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

Review of Individual Studies

Protocol N49-97-02-079: A double-blind, randomized, placebo and naproxen controlled study to evaluate the safety and pharmacokinetics of escalating doses of SC-58635 (800 mg bid and 1200 mg bid), in healthy subjects

Objective
This study was designed to investigate the high dose safety and pharmacokinetics of SC-58635 in healthy subjects. Secondary objectives were to determine the effects of high doses of SC-58635 on platelet and renal function as compared to placebo and naproxen.

Study design
This was a single-center, double-blind, randomized, placebo and active comparator-controlled multiple dose study. A group of 56 healthy subjects (age: 21-53 yrs) received SC-58635 800 mg BID, SC-58635 1200 mg BID, naproxen 500 mg BID or placebo BID. The study was designed in two tiers in which the first group of 28 subjects was administered either SC-58635 800 mg BID, naproxen 500 mg BID, or placebo BID (Tier I), followed by a safety review, and then the second group of 28 subjects was administered either SC-58635 1200 mg BID, naproxen 500 mg BID, or placebo BID (Tier II). In each of the Tiers, 12 subjects received SC-58635 (800 mg BID or 1200 mg BID), 8 subjects received naproxen 500 mg BID, and 8 subjects received placebo BID.

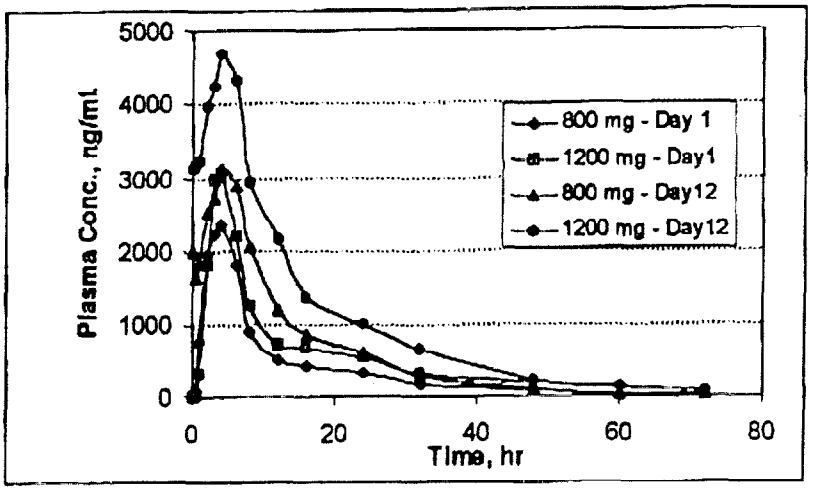
In Tier I, a single dose of SC-58635 800 mg, placebo, or naproxen 500 mg was administered followed by a 48-hour washout period. After the washout period, SC-58635 800 mg, naproxen 500 mg, or placebo was administered twice daily (BID) for nine and one-half consecutive days. Tier II was of similar design, except the SC-58635 dose was 1200 mg. Subjects had medium fat diet (~60g of fat/day) during the study period and medications were given 15 minutes after meal.

Blood samples:
Day 1: pre-dose and at 0.50, 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours postdose
Days 9 through 11: trough samples
Day 12: pre-dose and at 0.50, 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 48, 60, and 72 hours postdose

Assay:
Bound and unbound SC-58635 plasma concentrations was assayed using a HPLC method (LOQ: 10.0 ng/mL) to assess any shift in the ratio of bound to unbound as a result of protein binding saturation.

Results

The plasma concentration-time profiles for the 800-mg and 1200-mg doses on Days 1 and 12 are presented in the figure below. Trough concentrations on Days 9-12 are consistent with the hypothesis that steady state was reached before Day 12.



Mean pharmacokinetic parameter values are presented in the table below. Both mean Cmax and AUC were approximately dose proportional between the 2 doses used in this study. In general, this was also true for the parameters based on the unbound concentrations but the intersubject variability was much greater.

Parameter	Total plasma celecoxib conc. (ng/mL)		Unbound plasma celecoxib conc. (ng/mL)	
	800 mg	1200 mg	800 mg	1200 mg
Day 1				
AUC_{∞}, ng.h/mL	25361 (8270)	37722 (11580)	940.9 (428.0)	943.8 (607.5)
Cmax, ng/mL	2694 (504)	3668 (1595)	129.8 (94.5)	160.4 (160.8)
Tmax, hr	4.0 (1.1)	3.8 (1.2)	3.3 (0.6)	3.7 (1.7)
T1/2, hr	9.0 (2.8)	13.1 (6.3)	8.8 (4.1)	9.6 (3.2)
Day 12				
$AUC_{0\text{-}12}$, ng.h/mL	27035 (11541)	41960 (15766)	949.2 (627.4)	1537.8 (1060.3)
Cmax, ng/mL	3573 (1158)	5205 (1647)	151.2 (116.2)	237.0 (204.6)
Tmax, hr	3.9 (1.5)	4.0 (1.9)	3.3 (2.5)	3.7 (1.7)
T1/2, hr	8.2 (3.7)	11.4 (6.6)	7.7 (1.8)	10.8 (5.0)

Comments:

1. Note that this study was conducted under fed conditions (with medium fat content). Compared to data (Dose: 200 mg; AUC: 6894 ng.h/mL; Cmax: 952 ng/mL) generated in a previous study under fed conditions with medium fat content, the AUC values after a single

800 mg or 1200 mg dose were approximately dose proportional while the Cmax values were less than dose proportional.

2. The general safety and effect of celecoxib at 800 mg BID and 1200 mg BID on platelet aggregation and renal function are to be evaluated by the Medical Officer of HFD-550.

Protocol N49-99-02-123: An open label, randomized, two sequence, four period, replicated crossover study to compare the bioequivalence of two formulations of enteric coated diclofenac sodium 75 mg in healthy adult subjects

Background

Celecoxib Long-Term Arthritis Safety Study (CLASS 2) Protocol No. N49-98-12-102, was conducted to compare the incidence of clinically significant upper gastrointestinal adverse events associated with celecoxib 400 mg BID to that of diclofenac sodium 75 mg BID in patients with osteoarthritis or rheumatoid arthritis. For blinding purposes, CLASS 2 used the Searle formulation of diclofenac sodium comprised of a 75 mg enteric-coated diclofenac sodium core with placebo outer mantle (diclofenac/placebo). The sponsor needed to demonstrate the bioequivalence of diclofenac/placebo and Voltaren ®, each tablet containing 75 mg of diclofenac sodium.

Objective

Primary: To assess the in vivo bioequivalence of diclofenac/placebo relative to Voltaren with respect to diclofenac AUC(0-lqc) and AUC(0-inf).

Secondary: (a) To compare the rate of diclofenac absorption from each treatment, as determined by Cmax, Tmax, Tlag, and the ratio Cmax/AUC(0-inf) and (b) To determine intrasubject and intersubject variability for each treatment.

Study Design

This was an open label, randomized, four period, replicated crossover study. Thirty-six subjects (mean age: 34.8±8.2 yrs.; 26 M & 10 F) were randomized to receive four single oral doses of enteric coated diclofenac sodium 75 mg under fasted conditions. On Day 1 of treatment periods 1-4, subjects were administered 75 mg diclofenac as either diclofenac/placebo or Voltaren. The treatment sequences were either TRRT or RTTR. Diclofenac plasma samples were collected at predetermined intervals (0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10 and 12 hrs). A washout period of seven days separated each treatment.

Test Materials

Test product: Diclofenac sodium 75 mg enteric-coated core/placebo mantle tablets orally, Lot No. RCT 11010; Manufactured by G.D. Searle & Co.

Reference product: Voltaren (Diclofenac sodium) 75 mg enteric-coated tablets orally, Lot No. RCT 11011, Manufactured by Ciba Geigy (Vendor Lot No. LT5581)

Data analysis

Diclofenac $AUC_{(0\text{-}12)}$, $AUC_{(0\text{-}lqc)}$, $AUC_{(0\text{-}inf)}$, Cmax, T1/2, and $Cmax/AUC_{(0\text{-}inf)}$ with diclofenac/placebo (test) over Voltaren (reference) were compared using an analysis of variance

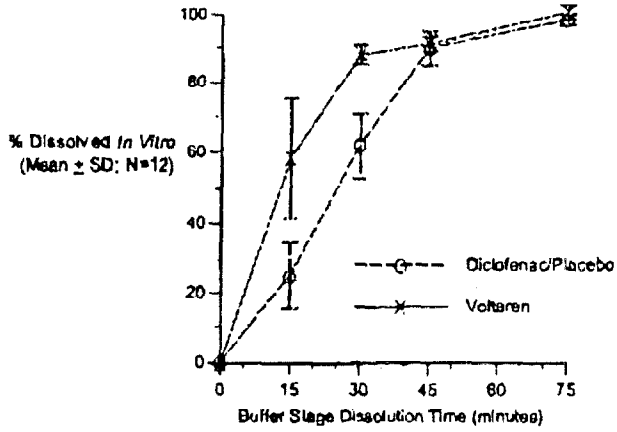
(ANOVA, SAS PROC MIXED) model with factors for treatment sequence, subjects (nested within sequence), period, treatment and carryover. If no statistically carryover effects were found, then the ANOVA model was repeated without the carryover factor, and sequence, period and treatment effects were determined. The p-values for the differences between the two formulations were obtained from the ESTIMATE statements in the ANOVA model.

The logarithmic least squares (LS) mean differences between the test and reference treatments were calculated. The 90% confidence intervals for these LS mean differences were also calculated. The ratio and the 90% confidence interval for the ratio of the test to reference treatments on the natural scale were obtained by exponentiating the logarithmic LS mean differences and the end points of the 90% confidence intervals for the mean differences. Bioequivalence of diclofenac/placebo and Voltaren was concluded for a pharmacokinetic parameter if the exponentiated confidence interval was contained in the acceptance interval (80%, 125%).

Results

In vitro dissolution

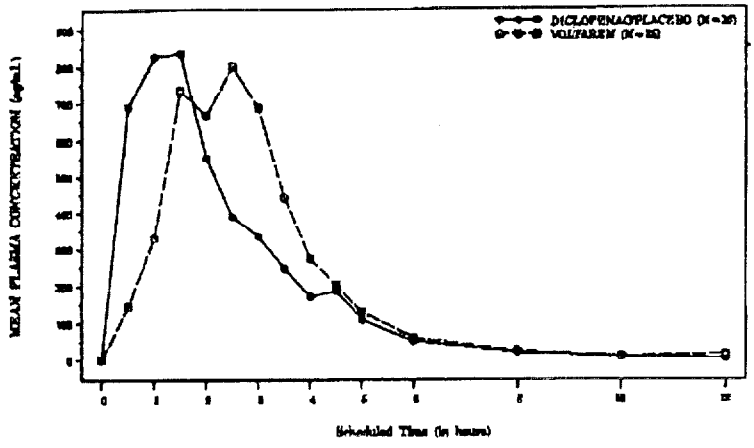
The results of in vitro dissolution analyses performed on 12 dosage units from each biostudy lot of diclofenac sodium tablets are presented in the table and figure below. During buffer stage dissolution, mean percentages of diclofenac dissolved from diclofenac/placebo tablets at 15 and 30 minutes were lower compared to those from Voltaren. After 45 and 75 minutes in buffer medium, however, both formulations demonstrated similar in vitro drug release profiles. (Reviewer's note: The acid stage dissolution test results were not provided.)



Buffer Stage Dissolution Time (minutes)	Percent Dissolved In Vitro, Mean ± SD (% CV)	
	Diclofenac/Placebo (N=12 Tablets)	Voltaren® (N=12 Tablets)
0	0	0
15	25 ± 9.6 (38)	58 ± 17 (29)
30	62 ± 9.2 (15)	88 ± 2.7 (3)
45	90 ± 5.0 (6)	91 ± 2.3 (3)
75	98 ± 1.6 (2)	101 ± 2.0 (2)

In Vivo Bioequivalence

Since this was a four period, replicated crossover study, 33 completed subjects provided two sets of observations for each of the two treatments. Three of the 36 subjects withdrew prior to study completion and provided only four sets of observations, two for diclofenac/placebo and two for Voltaren. Therefore, the analysis of bioequivalence was comprised of 35 subjects for diclofenac/placebo (Subject 0017 not included) and 35 subjects for Voltaren (subject 0027 not included). Analysis of intrasubject variability used data from 33 subjects who received replicate treatments.



AUC: The ratios and corresponding 90% confidence intervals for the exponentiated LS mean differences were given in the table below. The ratios indicate that differences in average diclofenac AUCs are <6% between diclofenac/placebo and Voltaren. The 90% CIs for diclofenac AUCs are within the standard acceptance range (80%, 125%).

Cmax: Bioequivalence for rate of diclofenac absorption was evaluated using Cmax (an indirect measure for absorption rate) and the ratio Cmax/$AUC_{(0\text{-}inf)}$ (an alternate metric for absorption rate). The ratios and corresponding 90% CIs for the exponentiated LS mean differences were outside of the 80-125% range for both Cmax and Cmax/$AUC_{(0\text{-}inf)}$ and did not fulfill the criteria for bioequivalence.

Mean diclofenac Tmax with diclofenac/placebo (1.44±0.98 hr) was shorter than that with Voltaren (2.25±1.49 hr). The mean lag period (Tlag) between dose and onset of diclofenac absorption was also shorter with diclofenac/placebo (0.83±0.73 hr) than that with Voltaren (1.91±1.56 hr).

Table: Geometric Mean PK Parameter Values and 90% CI for the ratio of T/R

Diclofenac PK Parameters (LSM)	$AUC_{(0\text{-}last)}$, (ng/mL)*hr (N=68)	$AUC_{(0\text{-}inf)}$, (ng/mL)*hr (N=67-68)	C_{max}, ng/mL (N=68)	$C_{max}/AUC_{(0\text{-}inf)}$, 1/hr (N=67-68)	$T_{1/2}$, hr (N=67-68)
Diclofenac/placebo	2233.14	2271.13	1483.60	0.66	1.81
Voltaren®	2323.42	2399.58	1996.90	0.85	1.73
Ratio (%)	96.114	94.647	74.295	77.176	105.078
90% CI (%)	(91.7, 100.7)	(91.2, 98.2)	(67.8, 81.4)	(71.8, 83.0)	(98.0, 112.7)

Intersubject and Intrasubject Variabilities

The intersubject and intrasubject variabilities are listed in the table below. For both diclofenac/placebo and Voltaren, the intersubject CVs in diclofenac AUC and Cmax were higher than the intrasubject CVs. Overall, both treatments demonstrated comparable intrasubject and intersubject variabilities in diclofenac AUC and C_{max}.

Table: Intersubject and Intrasubject Variabilities

	Intersubject Variability		Intrasubject Variability	
	Diclofenac/placebo	Voltaren	Diclofenac/placebo	Voltaren
$AUC_{0\text{-}lqc}$	27.3%	25.1%	11.0%	12.8%
$AUC_{0\text{-}inf}$	27.0%	23.3%	10.9%	10.6%
Cmax	37.0%	37.6%	27.0%	26.0%
$Cmax/AUC_{0\text{-}inf}$	26.3%	23.5%	22.0%	20.5%

Sponsor's Conclusion

Single oral doses of diclofenac/placebo 75 mg and Voltaren 75 mg were bioequivalent for extent of drug absorption, as determined by the 90% confidence intervals for diclofenac AUC(0-lqc) and AUC(0-inf) [90% CI: (91.7%, 100.7%) and (91.2%, 98.2%), respectively]. Bioequivalence was not established for Cmax as determined by the point estimate (74.3%) and 90% confidence interval (67.8%, 81.4%) for LS mean Cmax of diclofenac with test (diclofenac/placebo) relative to that with reference (Voltaren).

The sponsor considers lack of bioequivalency for diclofenac Cmax in the present study was not clinically important for the following reasons:

- Cmax from an enteric-coated tablet is highly dependent on gastric emptying time, which is known to vary widely both between and within subjects and on whether the product is given on an empty stomach or with food;
- Cmax from Voltaren (the reference treatment) was moderately variable, demonstrating an intrasubject CV of 26%;
- Diclofenac has a shallow dose response curve and wide therapeutic window; and
- For chronic drug administration, equivalent AUC values are clinically more relevant than equivalent Cmax values.

For diclofenac/placebo, intersubject CVs in diclofenac AUC (27%) and Cmax (37%) were higher than the intrasubject CVs (11% for AUC and 27% for Cmax). Overall, diclofenac/placebo and Voltaren demonstrated comparable intrasubject and intersubject variabilities in diclofenac AUC and Cmax.

Reviewer's comments:

1. Upon our request, the sponsor provided dissolution results from the acid stage which indicated that the enteric-coated diclofenac sodium tablets used in a safety trial did not dissolve in the acidic medium. No other supportive evidence was provided to demonstrate that the tablets remain intact in the stomach following oral administration.

2. Mean Cmax for the 75-mg diclofenac tablets used in the CLASS2 safety trial is similar to that observed with Voltaren tablets at the 50-mg dose level (mean Cmax: 1499±282 ng/mL) seen in a previous study conducted by Ciba-Geigy (Report # 82014).

3. Diclofenac 75-mg tablets used in the CLASS2 safety trial were not bioequivalent to the Voltaren 75-mg tablets with respect to Cmax. The sponsor considers this not clinically important. We disagree with the sponsor in this regard since there is no scientific evidence to rule out Cmax as an important parameter related to safety.